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Intrauterine rubella virus infection despite expected maternal immunity

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DOI: <https://doi.org/10.1007/bf01708631>

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ZORA URL: <https://doi.org/10.5167/uzh-155672>

Journal Article

Published Version

Originally published at:

Bossart, W; Nadal, D (1998). Intrauterine rubella virus infection despite expected maternal immunity. *European Journal of Clinical Microbiology Infectious Diseases*, 17(8):597-599.

DOI: <https://doi.org/10.1007/bf01708631>

Table 1 Clinical and laboratory findings in patients with HIV infection and periungual erythema

Patient no.	Age in years/sex	Focus of infection	>1x*	Mode of transmission	CDC classification	CD4+T cell count in μ l	HIV viral load (copies/ml)	HCV anti-bodies
1	36/m	F/T/P	yes	iv	C3	160	23993	pos
2	40/m	T	no	iv	B1	608	3847	pos
3	35/f	T	no	iv	B3	190	793404	pos
4	32/m	T/P	no	iv/msm	C3	100	413	pos
5	31/f	F/P	yes	iv	C3	157	750000	pos
6	30/f	T/P	yes	iv	B2	374	766	pos
7	38/m	F	yes	iv	B3	260	<244	pos
8	33/m	F	no	msm	A2	370	38515	neg
9	39/m	T	no	iv	B3	45	122085	nd
10	38/f	F	yes	iv	C3	57	15474	prob
11	58/m	T/P	no	bi	C3	5	169254	neg
12	33/m	T	no	iv	C3	30	40271	pos
13	34/m	F	no	iv	C2	260	<274	pos
14	31/m	T/P	yes	iv	B3	119	<418	pos
15	35/m	T	yes	hetero	B3	170	206167	neg
16	29/f	F/P	yes	iv	B2	310	na	na
17	56/m	F	no	msm	B2	270	nd	neg
18	57/m	T	no	msm	C3	20	45060	neg
19	28/f	F	no	iv	A1	851	1329	pos
20	33/m	F/P	no	iv	C3	135	165616	na
21	36/f	F/T/P	yes	iv	C3	95	4467	pos

* Diagnosis was established in more than one consultation

bi, bisexual; CDC, Centers for Disease Control; F, fingers; HCV, hepatitis C virus; hetero, heterosexual intercourse; iv, intravenous drug abuse; msm, men having sex with men; na, not available; nd, not done; neg, negative; P, palmar erythema; pos, positive; prob, probable; T, toes

these three patients periungual erythema was seen only once, and in two of them it disappeared before the next follow-up visit. However, it is also possible that the serological test for HCV was falsely negative [6]. All patients described by Pechère et al. [2] were intravenous drug users or alcohol abusers. Interestingly, all of our patients who were intravenous drug users had positive serological tests for HCV. There was no correlation between diagnosis of the periungual erythema and the activity of the HIV infection expressed by the actual viral load.

We conclude that periungual erythema in HIV-infected patients is most often associated with HCV infection with or without concomitant activity and non-virus-induced chronic liver disease. Other associations are suggested, especially in transient periungual erythema. Possibly, non-organ-specific autoantibodies in HIV infection [7] play a role in the pathogenesis of periungual erythema, reflecting the large spectrum of antibodies found in HIV-infected patients.

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Intrauterine Rubella Virus Infection Despite Expected Maternal Immunity

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Screening for immunity against the rubella virus is an essential part of the prenatal care of pregnant women.

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Table 1 Rubella-specific antibodies in the sera of the mother and her infant at different points in time

Time antibody test performed	Mother			Infant		
	IgG (IU/ml)	IgM	NT ^a	IgG (IU/ml)	IgM	NT
First trimester of pregnancy	195	neg	0	n.d.	n.d.	n.d.
At birth/delivery	149	neg	0	171	neg	0
3 months after birth	n.d.	n.d.	n.d.	43 ^b	neg	+ ^b
Before vaccination ^c	136	neg	++	0	neg	0
1 month after vaccination	188	neg	++	98	pos	++

^a Neutralisation of rubella virus by serum diluted 1:10

^b The child received intravenous immunoglobulins on the second day of life

^c Mother and infant were vaccinated with live attenuated rubella virus 15 months after birth
n.d., not done; neg, negative; pos, positive; NT, neutralising antibodies; 0, no neutralisation; +, weak neutralisation; ++, strong neutralisation

Infection of pregnant women who were expected to be immune to rubella, with subsequent transmission of the pathogen to the foetus, has been reported [1]. We present a case of rubella infection in the full-term infant of a seropositive mother who lacked neutralising antibodies. Our observation challenges immunity screening on the basis of mere antibody quantitation.

A newborn girl was referred to the University Children's Hospital, Zurich on the first day of life because she had petechiae, severe thrombocytopenia ($13 \times 10^9/l$), and ventricular extrasystoles. Neonatal alloimmune thrombocytopenia was diagnosed. Thrombocytes and immunoglobulins were infused. The infant's cardiac arrhythmia resolved spontaneously within 2 days.

Rubella virus was isolated in shell vial cultures of RK-13 rabbit kidney cells from throat swabs and urine collected on the infant's second day of life. Throat swab and urine samples were tested in parallel and in duplicate; no other samples tested positive for rubella virus the same working day. The immunofluorescence assay was validated by an inactivated positive control slide; no rubella virus was actively cultured in the laboratory during the relevant time period. Thus, mixing of the clinical samples is unlikely, and the possibility of laboratory contamination can be ruled out. The child showed no clinical or radiological signs of congenital rubella and developed normally. Viral cultures performed 3 weeks after birth were negative.

Rubella antibody determinations were performed initially by an external laboratory (IMX system; Abbott; Switzerland) and later by our own laboratories (Access system; Sanofi Pasteur Diagnostics, Switzerland). The sensitivity and specificity of the appropriate IgG tests were 99.7% and 98.9%, respectively, for the IMX system and 99.37% and 99.37%, respectively, for the Access system. For IgM confirmatory tests, the Sorin μ -capture enzyme immunoassay (EIA) (Sorin Biomedica; Italy) was used (sensitivity, 99.7%; specificity, 99.9%). The mother had not been immunised but

was shown to be seropositive for rubella virus by both laboratories. Sera collected from the mother during the first trimester of pregnancy and at delivery and from the infant on her second day of life prior to immunoglobulin infusion contained rubella-specific IgG and no specific IgM (Table 1). However, none of the sera contained neutralising antibodies, as demonstrated in vitro [2] using the Thomas laboratory strain of rubella virus. In contrast, the child's serum collected at age 3 months showed neutralising activity, which apparently originated from the infused immunoglobulins since the titre of specific IgG had dropped markedly. Investigation of the immune response to live attenuated rubella vaccine (strain Wistar-RA 27/3) 15 months after birth revealed a slight increase of specific IgG levels in the mother and seroconversion for IgM and IgG in the child. Moreover, the maternal pre-immunisation serum and the post-immunisation sera of both mother and child strongly neutralised rubella virus.

In this case the rubella infection would have gone unrecognised if neonatal alloimmune thrombocytopenia with petechiae had not necessitated tests for intrauterine infection. Isolation of rubella virus from two different body sites of the 2-day-old infant suggests an intrauterine infection, which seems to have been facilitated by the absence of maternal neutralising antibodies and to have occurred shortly before birth. Moreover, this infection seems to have resulted in the subsequent appearance of neutralising antibodies in the mother. The infused immunoglobulins may have contributed to clearing the virus and impeding a serologic response in the child [3, 4].

In most countries immunity to rubella virus is determined solely on the basis of quantitative IgG antibody determination. However, in a few countries such as Germany, IgG quantitation is combined with haemagglutination inhibition tests, which may correlate with neutralising antibodies [5]. As shown by our case, a functional test for determining the appropriate neutralising capacity of rubella antibodies has merit.

However, the addition of a neutralisation test to the antibody quantitation test to determine resistance to rubella in pregnant women would result in a considerable increase in testing and costs. Because the haemagglutination inhibition test is less demanding with respect to time and technical skills, it offers a more acceptable cost-to-benefit ratio than the classical neutralisation test. Additional studies are required to estimate the proportion of women who have EIA-positive, non-neutralising antibodies. This proportion may depend on the rates of natural infection and vaccination and, thus, may vary from country to country.

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